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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/066,255	04/24/98	BUECHLER	K 234/116

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EXAMINER	
GARCIA, M	
ART UNIT	PAPER NUMBER
1627	12

DATE MAILED: 04/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/066,255	Buechler et al
Examiner	**Group Art Unit**
Maurie E. Garcia, Ph. D.	1627

☒ Responsive to communication(s) filed on *Jan 11, 2001*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *23-35* is/are pending in the applicat

Of the above, claim(s) *23-27, 29, 31, 33, and 35* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *28, 30, 32, and 34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The response filed January 11, 2001 is acknowledged. No claims were amended, added or cancelled. Currently, claims 23-35 are pending.

2. This application contains claims 23-27, 29, 31, 33 and 35 drawn to an invention nonelected with traverse in Paper No. 5. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Maintained Rejections
Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28, 30, 32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims contain the term "ligand analogue", which is deemed to be indefinite. It is not clear what are the similarities and differences between the ligand and the ligand analogue; that is, how "analogous" must these two compounds be? Thus, it is impossible

to determine the metes and bounds of the invention and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Response to Arguments

5. Applicant's arguments filed January 11, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

6. Applicant argues that "ligand analogue" is definite (Response, pages 2-3). However, the examiner maintains that this tem makes it impossible to determine the metes and bounds of the invention. Applicants cite a dictionary giving the definition analogue to be "something that is analogous or similar to something else" (Response, page 3, top). The question at hand is not what the term means but the fact that it is a relative term. This terminology simply does not provide a standard for ascertaining the requisite degree of "analogy" applicant intends. It is unclear how "analogous" two compounds must be to be considered "analogues" of each other.

7. Also note that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, with respect to applicants citation of two issued US patents (Response, page 3, top), it is well settled that whether similar claims have been allowed to others is immaterial. See *In re Giolito*, 530 F.2d 397, 188 USPQ 645 (1976). The examiner

maintains that in the instant case, the use of the term "ligand analogue" is deemed to be indefinite.

Maintained Rejections
Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 30 and 34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Margaron et al (J. Photochem. Photobiol. B 1992-on PTO-1449, Paper No. 8) in view of Renzoni et al (US 5,135,717) further in view of Freytag (US 4,434,236).

Margaron et al teach water-soluble hybrid phthalocyanine derivatives (see Figure 1). The compounds taught by the reference consist of phthalocyanines where at least two of the four pyrrole moieties comprise a different number of rings (see in Figure 1, compounds labeled **M-N_2SB_2P** (cis and trans)). The photodynamic properties of the compounds are studied in biological systems (see Abstract). The compounds have superior absorption properties due to "the perturbation of the (na)phthalocyanine D_{4h} symmetry and the modification of the acennalation" (see page 188, 1st two paragraphs). Margaron et al lacks the teaching of using these compounds in a conjugate.

However, use of phthalocyanine deivatives in conjugates was well known in the art at the time of filing. Renzoni et al teach water-soluble phthalocyanine derivatives (see column 3, lines 29-55) that read directly on those of the instant claims. These phthalocyanines are conjugated to biologically active agents such as antibodies (column 39, lines 1-25), peptides or nucleotides (see claim 3 of the reference). The conjugates can be used in biological assays (see Example 16, column 39). The Renzoni reference lacks the specific teaching of a competitive assay as recited in the claims.

However, one of ordinary skill in the art would know that such labeled antibodies could be used in a competitive assay, because such assays were very well known in the art at the time of filing. For example, Freytag teaches an assay that is the same as the one claimed, except for the fact that Freytag uses different labels for the antibodies than the ones of the instant claims (see Abstract, Examples and claims 1-7 of the reference).

However, Freytag does discuss that fluorophores can be used for labeling the antibodies (column 3, lines 43-48).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the water-soluble hybrid phthalocyanine derivatives of Margaron et al in a conjuagate, as taught by Renzoni et al, and to further use these compounds as the fluorescent tags in the method of Freytag. A person of ordinary skill in the art would have been motivated to make such a substitution to use a fluorophore with "more ideal spectral properties" as taught by Renzoni et al (column 1, lines 49-52); specifically, the fluorophore of Margaron et al would have preferable properties based on its asymmetry.

11. Claims 28 and 32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Margaron et al (J. Photochem. Photobiol. B 1992-on PTO-1449, Paper No. 8) in view of Renzoni et al (US 5,135,717) and further in view of Freytag (US 4,434,236) as applied to claims 30 and 34 above, and further in view of Stanton et al (US 4,803,170).

The teachings of Margaron et al concerning water-soluble hybrid phthalocyanine derivatives are set forth *supra*. Also, the combination of Renzoni et al and Freytag teach that water-soluble phthalocyanine derivatives conjugated to biomolecules can be used in a competitive assay, as discussed *supra*. None of these references discloses the configuration of bound ligand analogue in step b (claim 28) and furthermore the prior binding to a solid phase (claim 32) recited in the instant claims.

However, one of ordinary skill in the art would know that such a configuration could be easily achieved, and would simply be a design choice in the creation of the assay set-up. Such assays were well known in the art at the time of filing. For example, Stanton et al discusses a competitive assay where the analyte conjugate and ligand/marker binding partner are both bound to a solid phase (Abstract and column 3). Most importantly, "excess analyte conjugate becomes sequestered...on a surface, where its marker activity can be read as an indication of analyte presence" (column 3, line 66 – column 4, line 1).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the water-soluble hybrid phthalocyanine derivatives of Margaron et al in a conjuagate, as taught by Renzoni et al, and to further use these compounds as the fluorescent tags in the method of Freytag. A person of ordinary skill in the art would have been motivated to make such a substitution to use a fluorophore with "more ideal spectral properties" as taught by Renzoni et al (column 1, lines 49-52); specifically, the fluorophore of Margaron et al would have preferable properties based on its asymmetry. One would be additionally motivated to use the bound configuration of Stanton et al to create a more facile assay, as taught by the reference (column 1, lines 9-18).

Response to Arguments

12. Applicant's arguments filed January 11, 2001 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

13. In response to applicant's arguments, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). As discussed in the rejection above, the examiner's position is that the *combined* teachings of the references render applicant's invention prima facie obvious to one of ordinary skill.

14. Specifically, in applicant's discussion of the Margaron et al reference, applicant argues several points. First, applicant indicates that the reference teaches the use of phthalocyanine derivatives in cancer phototherapy and appears to imply that these teachings make this non-analogous art. However, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teaching of phthalocyanine derivatives for phototherapy (i.e. uptake in cells) is pertinent to the

problem of using labels in a biological assay as both involve binding of a labeled compound to a target and absorption properties of such labels. "A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."; In re Clay, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) and Wang Laboratories Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993).

15. Second, applicant states that "the Margaron et al reference does not support the Examiner's contention" (Response, page 4, bottom) that the compounds of the reference have superior absorption properties due to "the perturbation of the (na)phthalocyanine D_{4h} symmetry and the modification of the acennalation" (see page 188, 1st two paragraphs of Margaron et al). Applicants quote Margaron et al, page 188, which states:

"[b]ecause of the perturbation of the (na)phthalocyanine D_{4h} symmetry and the modification of the acennalation, the degree of the sulfonation of the different condensation products can readily be deduced"

However, this quotation of Margaron et al ***in full*** states:

"[b]ecause of the perturbation of the (na)phthalocyanine D_{4h} symmetry and the modification of the acennalation, the degree of the sulfonation of the different condensation products can readily be deduced from the electronic spectra which shift from maxima around 680-720 nm, in the case of the trisulfonated M-NSB_3P, to major absorption bands between 720-770 nm, in the case of monosulfonated M-N_3SBP."

Thus, this shift in absorption maxima is what is being referred to by the examiner as superior since the reference teaches absorption above 680 nm is preferred (see page 188, top, of the reference).

16. Applicant states that Margaron et al teach that their phthalocyanine derivatives are useful because they "can readily absorb light toward the red end of the physical spectrum, allowing the use of a light wavelength that penetrates deeper into tissue" (Response, page 4, middle). Although this is true, again the full teachings of Margaron et al are not considered. Consider the following from Margaron et al (page 187 bottom through page 188, top):

"The rationale for the latter [molecules that absorb more strongly towards the red end of the spectrum] is that light above 680 nm allows for deeper penetration into biological tissues *as well as the availability of less expensive and more reliable light sources at these higher wavelengths*" (emphasis added)

Thus, Margaron et al teach ***two*** advantages for absorbing toward the red end of the spectrum. It was well known in the art at the time of filing that absorbing toward the red end of the spectrum is advantageous because low cost semiconductor lasers can be used (see additionally, Renzoni et al columns 1-2). Thus, the use of the phthalocyanine derivatives of Margaron et al as labels in a conjugate (as taught by Renzoni et al) would be obvious to make use of such advantages.

17. Note, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would

have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references is being able to use "a less expensive and more reliable light source" as taught by Margaron et al.

18. Concerning applicant's argument that the reference is "silent as to the fluorescence properties of such phthalocyanine derivatives" (Response, page 5), the examiner would like to make several points. First, as set forth above, Margaron et al **does** teach the absorption maxima (which is related to fluorescence) for hybrid phthalocyanine derivatives that read on those claimed. Also, the compounds of the reference meet **all** of the limitations of the "water-soluble hybrid phthalocyanine derivatives" of the claims and thus would have the same properties of such compounds. Fluorescence is a property that depends on the physical structure of a compound and thus would be an intrinsic property of the molecule itself. Also, it is well known in the art that phthalocyanine derivatives are fluorescent, see teachings of Renzoni et al for example.

19. Further, "the fluorescence properties of such phthalocyanine derivatives" are ***not being claimed***. There is nothing in the instant claims with respect to a specific stokes shift and/or intensity or any other particulars of the fluorescence of the molecule. In fact, there is nothing in the instant claims that limits them to fluorescence at all. The claims merely state "generating a detectable signal". Although the claims are interpreted in light of the specification, limitations

from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

20. Moreover, applicant also states that "the water soluble phthalocyanine derivatives of the instant invention have advantageously large stokes shifts and intensities" (Response, page 2, top and elsewhere). It appears as if applicant may be trying to imply that the claimed method produces unexpected results. However, objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results... See, for example, In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence"). Lastly, any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (In MPEP § 716.02). Also, applicant's arguments do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

21. Applicant argues that Margaron et al "actually teaches away from using water soluble molecules...stating that amphiphilic molecules are superior to hydrophilic molecules in phototherapy applications" (Response, page 5, 1st full paragraph). The examiner respectfully disagrees that this is a teaching away from the claimed invention. Although Margaron et al does

teach that an amphiphilic molecule produces the best activity, the reference also teaches that hydrophilic molecules will work. More importantly, Margaron et al also teaches that the hydrosolubility of sulfonated phthalocyanines "makes them suitable for biological evaluation" (Margaron et al, page 188, 1st full paragraph). Second, the claimed invention is not phototherapy and the rejection is based on the combination of teachings, i.e. that it would be obvious to one of ordinary skill to use the hybrid phthalocyanine derivatives of Margaron et al as a label in the conjugates of Renzoni et al. Again, Margaron et al teach "hybrid phthalocyanine derivatives" that meet **all** of the limitations of the instant claims and thus these compounds would have the same properties of the claimed compounds with respect to solubility as well. Finally, amphiphilic molecules contain both polar, water-soluble groups and nonpolar, water-insoluble groups and can be considered as having solubility in both media.

22. Applicant argues that there is "nothing in the Renzoni et al reference to suggest that properties rendering molecules useful in cancer phototherapy would make those molecules useful as conjugates for use in assays" (Response, page 6). The examiner respectfully disagrees. The reference teaches that absorbing toward the red end of the spectrum is advantageous because low cost semiconductor lasers can be used (see columns 1-2 of Renzoni et al, esprecially column 1, lines 39-45 and column 2, lines 1-3). Margaron et al also contains such teachings (see paragraphs 15-17 above). Thus, using molecules that absorb at such wavelengths would be obvious and Margaron et al teach such compounds. Again, Margaron et al teach "hybrid phthalocyanine derivatives" that meet **all** of the limitations of the instant claims and thus these

compounds would have the same properties of the claimed compounds. Also, Renzoni et al teach the use of water-soluble phthalocyanine derivatives as fluorescent labels in conjugates. The examiner recognizes that the phthalocyanine derivatives of Renzoni et al are not "hybrid phthalocyanine derivatives" as instantly defined; however, they possess a high degree of structural similarity to those claimed. As stated above, the motivation to use the "hybrid phthalocyanine derivatives" of Margaron et al in the conjugates of Renzoni et al is to achieve the beneficial result of being able to use "a less expensive and more reliable light source" as taught by both Margaron et al and Renzoni et al.

23. Applicant argues that the teachings of Freytag and Stanton et al "do not overcome the deficiencies of the Examiner's faulty *prima facie* case of obviousness" and that the references "merely describe assay methods generally" (Response, page 6, 1st full paragraph). However, the examiner maintains that such assay methods were extremely well known in the art and to use any conjugate in such a method would be obvious. Various configurations would simply be a design choice in the creation of the assay set-up and do not appear to be critical to the patentability of the claimed invention.

24. Finally, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (Response, page 6, 2nd paragraph), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within

the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner maintains that the combined teachings of the cited references indicate information that was within the level of ordinary skill and render the claimed invention prima facie obvious.

Status of Claims/ Conclusion

25. No claims are allowed.

26. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie E. Garcia, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 8:30 to 6:00.

28. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Maurie E. Garcia, Ph.D.
March 28, 2001